

# Features of Cytokine Status in Children with Type 1 Diabetes Who have Suffered COVID-19 Infection

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**Abstract** To study the features of serum cytokines in children with type 1 diabetes mellitus who have suffered COVID-19 infection. For our study, 140 children with type 1 diabetes who suffered from COVID-19 were treated in the children's department of the RSNPMC endocrinology aged 2 to 18 years. The comparison group was 65 children with type 1 diabetes, a group of 15 practical healthy children matched for age and sex without any signs or symptoms of cardiovascular disease was used as a control. The work uses immunological research methods and statistical research methods. In patients with diabetes mellitus and cardiac complications, there were multidirectional changes in a number of pro-inflammatory cytokines: a decrease in the level of Il-17p, with an increased content of Il 1.10 and TNF-a.

**Keywords** Type 1 diabetes mellitus, Children interleukins, COVID-19

## 1. Relevance

Currently, SARS-CoV-2 infection is also a potential trigger for the development of type 1 diabetes mellitus in children, which represents the most common chronic metabolic disorder in the pediatric population. There is growing evidence that many patients with COVID-19 may experience a wide range of post-acute consequences, including cardiovascular complications [2]. COVID-19 causes not only viral pneumonia, but also many extrapulmonary complications, such as cardiovascular or cerebrovascular diseases. COVID-19 can excessively stimulate the sympathetic system and cause an inflammatory cytokine storm and a state of hypercoagulopathy. These mechanisms can cause irreversible damage to the cardiovascular or respiratory system even after recovery from COVID-19. [5].

Type 1 diabetes mellitus (SD1) is one of the most common chronic diseases affecting children. In this disease, various micro- and macrovascular complications are often observed, which leads to at least a 10-fold increase in cardiovascular morbidity compared to healthy people of the same age [1,3]. Diabetes mellitus is characterized by a variety of cardiovascular complications. Currently, there is strong evidence on the role in the formation of chronic heart failure of cytokines such as interleukin-1 (IL-1), tumor necrosis factor-a (TNFa), interleukin-6 (IL-6), manifested by the gradual destruction of the extracellular collagen myocardial matrix followed by cardiomyocyte hypertrophy and cavity dilation [6].

Diabetes mellitus is characterized by various cardiovascular complications including myocarditis. Myocarditis occurs as

a result of a COVID-19 infection. Pathogenetically, myocarditis leads to diastolic and systolic dysfunction, and finally to congestive heart failure [2,7].

Over the past 10 years, numerous data have been accumulated on the role of the cytokine system in the pathogenesis of cardiovascular disease. Cytokines are a group of polypeptide mediators of intercellular interaction. Cytokine-induced processes promote myocardial remodeling with irreversible cavity dilation and hypertrophy, process activation processes of cardiomyocyte apoptosis [1,3]. Currently, there are strong data on the role in the formation of chronic heart failure of cytokines such as interleukin-1, tumor necrosis factor-a (TNF-a), interleukin-6, manifested by the gradual destruction of the extracellular collagen myocardial matrix followed by cardiomyocyte hypertrophy and cavity dilation [4,5].

## 2. Purpose of the Study

To study the features of serum cytokines in children with type 1 diabetes mellitus who have suffered COVID-19 infection.

## 3. Research Materials and Methods

For our study, 140 children with type 1 diabetes who suffered from COVID-19 were treated in the children's department of the RSNPMC endocrinology aged 2 to 18 years. The comparison group was 65 children with type 1 diabetes, a group of 15 practical healthy children matched for age and sex without any signs or symptoms of cardiovascular disease was used as a control. The work uses immunological research methods and statistical research methods.

## 4. Results and Discussion

As can be seen from the data presented in Table 1, in patients with diabetes mellitus who have undergone COVID-19 infection, there was no statistically significant difference in age, duration of diabetes mellitus and gender compared to the group without COVID-19 infection.

During the study of cytokine content in children with type 1 diabetes mellitus who underwent COVID-19 infection, multidirectional changes were obtained. Thus, the level of IL-17 in patients with diabetes mellitus who underwent COVID-19 was infectious compared to the comparison group. The concentration of some pro-inflammatory cytokines was higher in patients with diabetes mellitus, especially significant in the presence of transferred COVID-19 Infections. When comparing two groups of patients, we found that in the group with children with diabetes mellitus who had undergone COVID-19, the infection exceeded the level of TNF a. It is noteworthy that the concentration of TNF-a in patients with diabetes mellitus without COVID-19 infection did not differ from the indicator of the control group, on the basis of this we consider it possible to consider the concentration of this cytokine as a specific marker of diabetic myocardial injury.

There was a tendency to increase the content of IL-17 in the blood serum of the studied patients, but no statistically significant difference between the groups was detected.

In patients with diabetes mellitus, the concentration of anti-inflammatory IL-10 increased depending on the presence of COVID-19 infection. Thus, in this group, its content exceeded the control and comparison groups

**Table 1.** Cytokine scores in the study group

Key figure	Main group	Comparative group	Control group
IL-1	9,8±0,6	4,5±0,3	3,8±0,3
IL-17	6,7±0,48	7,7±1,1	6,7±0,5
IL-10	7,2±0,75	2,1±0,3	0,84±0,1
TNF-a	7,4±0,54	3,4±0,6	2,7±0,2

Currently, the role of immune activation in the processes of progression of heart damage and the development of heart failure has been convincingly proven. A number of researchers have assigned the expression of pro-inflammatory cytokines to one of the main roles in the development and progression of CHF. According to various authors, the mechanism of action of pro-inflammatory cytokines consists of negative inotropic action, myocardial remodeling, impaired endothelium-dependent dilatation of arterioles and increased apoptosis cardiomyocytes.

An increase in IL-1 in patients with diabetes mellitus with COVID-19 infection is probably due to an increase in the receptor antagonist of this molecule, which, for example, is observed in patients with CHF. IL 1-part regulation of endothelial and blood coagulation functions, induces procoagulant activity, synthesis of pro-inflammatory cytokines and expression of adhesive molecules on the endothelial surface, which is one of the mechanisms of progression of

vascular damage in DM, and as a result, myocardial damage.

The most significant results on the effect of pro-inflammatory cytokines on the myocardium were obtained for TNF-a. Thus, the content of this cytokine correlates with the severity of angina pectoris in patients with diabetes mellitus and the functional class of heart failure. In our study, a significant increase in TNF-a content was detected in patients with diabetes mellitus type 1 who underwent COVID-19, which can probably serve as both one of the causes of the development of myocarditis and be a prognostic ally unfavorable factor for the progression of myocardial damage.

Differentiation of IL-17 occurs independently of T-1 and T-2. IL-17 shows pronounced pro-inflammatory activity, is able to induce synthesis of various inflammatory mediators, including TNF-a, 1 and Il-6, thereby contributing to the development of autoimmune pathological reactions. In our study, the concentration of Il-17 was lower than the main group and is probably due to the lack of autoimmune mechanisms in the development of this complication of diabetes mellitus.

The content of anti-inflammatory IL-10 was increased in the main group of patients and increased in parallel with the formation of heart damage and an increase in the level of provospal cytokines.

Thus, in patients with type 1 diabetes mellitus, there was an increase in interleukins 1, 10, and TNF, while an increase in the concentration of these cytokines was more pronounced in the presence of a previous COVID-19 infection. In patients with myocarditis, an increase in the concentration of TNF-a was recorded compared to a cohort of healthy individuals and patients with type 1 diabetes without COVID-19 infection. The relationship of serum IL-17 with the presence of diabetes mellitus and myocarditis was not detected.

## 5. Conclusions

In patients with diabetes mellitus and cardiac complications, there were multidirectional changes in a number of pro-inflammatory cytokines: a decrease in the level of Il-17p, with an increased content of Il 1.10 and TNF-a. An increase in TNF-a concentration in patients with type 1 diabetes mellitus who underwent COVID-19 infection was accompanied by an increase in the level of anti-inflammatory cytokine Il 1.10.

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